Remarks/Arguments

Claims 42, 43, 54, 55 and 57-62 are under consideration. Claims 42, 43, 54, 55, and 57-62 have been canceled, without prejudice, as drawn to non-elected inventions. Applicants specifically reserve the right to pursue the subject matter of the canceled claims in one or more continuing applications. Claim 40 has been amended to more specifically claim the invention. Claims 50 and 52 have been amended to correct minor errors and informalities. New Claim 63 has been added to cover subject matter originally included in Claim 52. All amendments are fully supported by the specification as originally filed, and do not add new matter.

Restriction and Election of Species

Applicants note the finality of the restriction and election of species requirement.

Information Disclosure Statement

Enclosed is a Supplemental Information Disclosure Statement providing the publication dates for the publications numbered 17 and 21 in the Information Disclosure Statement filed on February 16, 2002. The current submission is in full compliance with 37 CFR 1.97(e).

Claim Rejections - 35 U.S.C. 112, first paragraph (Written Description)

Claims 40-41, 44-53, and 56 were rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the claimed invention. According to the rejection, the claims encompass "an infinite number of methods for identifying an infinite number of small organic compounds using an infinite number of target proteins and an infinite number of ligands." The Examiner adds that, based upon the working examples, it is not possible to determine *a priori* which "proteins," "ligands," "small organic molecules," "first and second functionalities" would be encompasses by the present

claims. Finally, the Examiner notes that "simply reciting a 'laundry list' of potential biological target molecules, chemically reactive groups and target proteins . . . is insufficient to teach the entire genus."

The Legal Standard

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See, e.g. Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

In Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), the Federal Circuit held that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or a recitation of structural features to the members of the genus, which features constitute a substantial portion of the genus. *Id.* 119 F.3d at 1569, 43 USPQ2d at 1406. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, & 1, 'Written Description' Requirement, 66 F.R. 1099, 1106 (January 5, 2001) (hereinafter "Written Description Guidelines") provide that applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or

disclosed correlation between function and structure, or some combination of such characteristics. Written Description Guidelines at 1106.

The Claimed Invention

It is axiomatic that the requirements of patentability, including the written description requirement, must be assessed with regard to the invention claimed.

The present invention is not directed to target proteins, ligands, or small organic molecules. Rather, the present invention concerns a broadly applicable screening method for rapidly identifying members of a library of small organic molecules that are capable of covalent binding to a chemically reactive group present on a target protein-ligand conjugate.

It is clear from the disclosure that this method can be used to identify small molecule ligands of "virtually any peptide or protein that comprises two or more amino acids and which possesses or is capable of being modified to possess a chemically reactive group for binding to a small organic molecule." (Page 8, lines 15-19.) While proteins of interest are listed on pages 8-9 and other locations in the application, the operability of the invention is not limited to any particular protein structure. The claimed method is suitable for identifying a small organic compound capable of binding to a pre-formed target protein-ligand conjugate, regardless of the actual identity of the protein or ligand present in the conjugate. This method, which can be repeated in an iterative process, yields organic molecules which exhibit progressively higher affinity for the target protein (see, e.g. the passage bridging pages 23 and 24 of the specification).

Similarly, the operability of the claimed invention is not limited to the identification of any particular small organic compound. The claimed method is suitable for screening any small organic compound present in a library, regardless of its overall chemical structure, as long as it contains a reactive group capable of forming a (second) covalent bond with a chemically reactive group on a target protein-ligand conjugate. Chemical classes of ligands are listed, for example, on page 17, lines 5-18, however, any small organic compound can be screened by the methods of the present invention, within or outside the specifically listed chemical classes, if a covalent bond can be formed

between such compound and a chemically reactive group on a target protein-ligand conjugate. As it is stated at page 17, lines 18-23: "In fact, virtually any small organic molecule that is capable of covalently bonding to a known chemically reactive functionality might find use in the present invention with the proviso that it is sufficiently soluble and stable in aqueous solution to be tested for its ability to bind to the biological target molecule."

The disclosure is also clear that those "of skill in the art will be capable of covalently linking a chemically reactive group-containing compound to a target biomolecule through virtually any type of covalent bond, including . . .disulfide bond . . .. (Passage bridging pages 13-14.) Although the nature of the covalent group is not critical, the disclosure provides an extensive listing of chemically reactive groups, e.g. at page, 9, lines 16-20; page 15, lines 3-13, and page 17, lines 5-23. Applicants also provide guidance for choosing compatible chemically reactive groups on the target proteins and ligands (see, e.g. page 16, lines 4-23 and the passage bridging pages 17-18). One of ordinary skill in the art would readily understand that similar flexibility exists in selecting compatible free chemically reactive groups on the protein-ligand conjugate and a library member, respectively.

The invention is further illustrated by a working example, where the target protein is a cysteamine-modified thymydilate synthase, and the ligands are aldehydes. The "site of interest" is the active site of the protein. The aldehyde functionality of the individuals ligands reacts with the primary amine group of the protein-bound cysteamine to yield an imine bond. Because this reaction is reversible, equilibrium will favor imine formation with the library member that had the highest intrinsic affinity for the active site of the protein. One skilled in the art would appreciate that the same type of chemical reaction could be used, for example, to build off of the ligand covalently bound to the cysteamine-modified thymydilate synthase, following the process claimed in the present application.

Proper Application of the Legal Standard

The Examiner's reasoning underlying the present rejection indicates that the Examiner erroneously applied the legal standard developed for assessing written

description for a genus of chemical entities (e.g. nucleic acid molecules or proteins) to an invention which provides a new screening assay. The Examiner has given no reason why one skilled in the art would not reasonably accept that the screening method of the invention can be performed with any target protein and any ligand, capable of forming any type of covalent bond, i.e. that applicants were in the possession of the invention at the effective filing date of the present application, within the full scope of the claims pending. Indeed, such reasons do not exist. The reactive groups and chemical reactions involved in the formation of the covalent bond between a target protein-ligand conjugate and a further ligand, as required by the claims, were well known in the art at the priority date of the present application, and are also detailed in the specification, including the references cited therein. There is no reason, and the Examiner certainly did not provide one, why these steps could not be performed with virtually any protein and any ligand, following well known steps and reactions of chemistry.

The burden is on the Examiner to provide specific reasons why Applicants did not provide sufficient written description for the invention claimed. It is submitted that the Examiner failed to provide such reasoning. Accordingly, the Examiner is respectfully requested to withdraw the present rejection, or, as a minimum, if the rejection is upheld, provide specific scientific reasoning why one skilled in the art would not accept that at the effective filing date of the present application applicants were in the possession of the invention as claimed.

Additional Remarks

The Examiner's statement that the claims include an "infinite number of methods" is clearly in error. In fact, the claims are directed to a particular, well defined method, which is applicable to a wide range of target protein-ligand conjugates and small organic compounds, without any limitation as to the number or type of atoms, etc., except the nature of reactive groups, which, as discussed above, is clearly disclosed in the specification.

As discussed above, the disclosure of specific protein or ligand structures is not needed for adequate written description. However, the Examiner's assertions that such

structures are missing are misplaced. The listing of specific target proteins, e.g. in the passage bridging pages 8 and 9, is equivalent with providing structures for the listed proteins, since such proteins, including their structures, were well known in the art at the priority date of the present application. Chemically reactive groups are also detailed.

Although complete ligand structures are not specifically disclosed, the ligands are sufficiently characterized to the extent necessary to perform the present invention, by listing exemplary chemical classes, and exemplary reactive groups that can bind to a compatible reactive group on the target protein, to form a covalent bond.

Applicants are at a loss to understand the Examiner's reference to the extensive teaching in the specification as a "laundry list" of potential biological target molecules, chemically reactive groups and target proteins. It is hard to imagine how else Applicants could provide guidance in the specification but by providing an extensive listing of exemplary embodiments within the scope of the invention.

Claim Rejections - 35 USC 102

THE REJECTION UNDER 35 U.S.C. 102(b) OVER PITNER ET AL. SHOULD BE WITHDRAWN

Claims 40-41, and 44-46 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Pitner et al. (U.S. Patent No. 5,367,058, issued November 22, 1994). According to the rejection, Pitner et al. teaches (a) a method for modifying antibodies, which anticipates claim 40; (b) a disulfide bond as a second covalent bond, which anticipates claim 41; (c) a fee thiol, which anticipates claim 44; (d) library members with thiols and disulfides, which anticipates claim 45; and (e) all library members with amides, which anticipates claim 46.

Applicants respectfully disagree and vigorously traverse the rejection.

A reference is anticipatory if it discloses each element of the claimed invention.

The invention claimed in Claim 40 of the present application, includes the following steps:

(a) screening a library of small organic compounds with a protein-ligand conjugate

comprising a free chemically reactive group under conditions such that at least one member of the library forms a covalent bond with the protein-ligand conjugate; and

(b) identifying a small organic compound that binds covalently to the chemically reactive group of the protein-ligand conjugate.

Pitner et al. concerns the modification of an antibody by a "modifying group" sufficiently proximate to the antigen binding site of the antibody such that a covalent bond may be formed between the modifying group and the antigen when it binds to the antibody. (See, e.g. column 2, lines 44-51.) Figure 1 illustrates a particular embodiment, in which an antigen, carrying a cleavable linking group that contains a modifying group for the antibody, is reacted with an NH_2 group on the antibody, near the antigen binding site. After the antigen has reacted with the antibody, the reactive group is cleaved from the antigen. This leaves the antibody with a modifying group in sufficient proximity to the antigen binding site such that a covalent bond between the antigen and the modifying group will occur upon reaction of the antigen and the antibody. The preferred antibody modifying group is a thiol group.

Pitner et al. discloses a modified antibody, which, using the terminology of the present application, can be viewed as a biological target molecule comprising a first reactive functionality (e.g. a thiol group). Pitner et al. discloses an antibody-antigen conjugate, in which the antigen is covalently linked to the antibody. However, the antibody antigen conjugate, as formed, does not contain a free chemically reactive group. Although upon cleaving the modifying group from the antigen, e.g. as shown in Figure 1 of Pitner et al., the antibody-antigen conjugate may be viewed as containing a chemically reactive group, however, the chemically reactive group is not attached to the antigen (ligand), as required by the current language of Claim 40, and as it was inherent in the claim language even before the current amendment, rather to the antibody (target protein). Accordingly, Pitner et al. does not describe a target protein-ligand conjugate with a free reactive group attached to the ligand present in the conjugate, or the screening of a library of small organic compounds with such conjugate.

Furthermore, Pitner et al. does not describe the identification of a small organic

compound that binds covalently to the chemically reactive group of the protein-ligand conjugate (step b) of Claim 40). Indeed, antibodies are raised to antigens, therefore, the identification of an antigen bound to an antibody is not required.

Since Pitner et al. fails to disclose all elements of Claim 40, the present rejection on the ground of alleged anticipation should be withdrawn.

As Claim 40 is not anticipated, dependent Claims 41, 44, 45, and 46, which carry the recitations of Claim 40, are not anticipated for the same reasons.

THE REJECTION UNDER 35 U.S.C. 102(b) OVER JANDA ET AL. SHOULD BE WITHDRAWN

Claims 40-41, 44-46 and 56 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Janda et al. (PNAS, March 1994, 91:2532-2536).

According to the rejection, Janda et al. teaches a method for screening a combinatorial antibody library for enzymatic activity, which anticipates claim 40. The Examiner specifically refers to Figures 1-2, as allegedly showing reaction of a compound 1 (a ligand) with BSA (the target protein), wherein compound 1 contains a second reactive functionality (N-hydroxysuccinimide ester) that reacts with a first reactive functionality (an amino group) on the target protein, to form a covalent bond, leaving a chemically reactive group (a disulfide bond) for covalent attachment to the antibody, wherein at least one member of the library forms a second covalent bond with the target protein-ligand conjugate.

One fallacy in this analysis is that the compound of formula 1 is not considered a ligand by the definition of the present application. The disclosure is clear that ligands are compounds that have an inherent affinity to specific sites on target biological molecules, such as proteins. For example, at page 3, lines 25-31, the specification states:

> "The herein described approaches allow one to quickly screen a library of small organic compounds to unambiguously identify *those that have affinity* for a particular site on a biomolecular target. Those *exhibiting*

affinity for interacting with a particular site are capable of forming a covalent bond with a chemically reactive group at that site, whereby small organic compounds capable of covalent bond formation may be readily identified and characterized" (Emphasis added.)

According to page 25, lines 3-12:

"In a typical experiment, individual libraries each consisting of a set of ten different aldehydes chosen to be of similar reactivity and structure will be mixed with the cysteamine-modified protein in aqueous buffered solution. Initial experiments will dictate the concentration of aldehydes used; at first, a wide range of different concentrations will be tested. During this time the aldehyde functionality of individual library members will react with the primary amine group of the protein-bound-cysteamine to yield an imine. Because this reaction is reversible, equilibrium will favor imine formation with the library member *that has the highest intrinsic affinity for the active site of the protein.* (Emphasis added.)

Compound 1 of Janda et al. does not have an affinity for a particular site on BSA. The racemic reagent 1 is coupled to BSA by a chemical reaction, but does not have an inherent affinity (binding ability) to BSA, therefore, it is not a "ligand" of BSA. Accordingly, Janda et al. does not disclose target protein-ligand conjugates, as defined in the present application, or any screening assays with such target protein-ligand conjugates.

Since Janda et al. does not disclose all elements of the process claimed in Claim 40, it does not anticipate that claim.

Furthermore, Janda et al. describes the selection of catalytic antibodies from combinatorial antibody libraries. In the course of this process, the racemic reagent 1 coupled to BSA is used as a probe for cysteine groups in antibody-binding sites through the process of disulfide interchange. The Examiner's reference to the disulfide bond as a "chemically reactive group" (or "free chemically reactive group" with the terminology of Claim 40) is believed to be in error. The disulfide linkage is a chemical bond, and not a free chemically reactive group Indeed, while in the present invention, the ligand in the protein-ligand conjugate remains intact while a further ligand forms a covalent bind with the free chemically reactive group present in the first ligand, in the process taught by

Janda et al., at least part of the first ligand leaves and is replaced by a second ligand, through the process of disulfide exchange. This is a fundamentally different process from that claimed in the present application, therefore, Janda et al. does not anticipate Claim 40.

Since Claim 40 is not anticipated, dependent Claims 41, 44, 45, and 46, which carry the recitations of Claim 40, are not anticipated for the same reasons. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections - 35 USC 103(a)

THE REJECTION UNDER 35 U.S.C. 103(a) OVER PITNER ET AL. AND LOO ET AL. SHOULD BE WITHDRAWN

Claims 40-41, and 44-49 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Pitner et al. (U.S. Patent No. 5,367,058) and Loo et al., Mass Spectrometry Reviews, 1997, 16, 1-23.

According to the rejection, Pitner et al. teaches all the limitations of claims 40-41, and 44-46, "consequently also renders obvious claims 40-41 and 44-46." With regard to Claims 47 and 48 of the present application, Lee et al. was cited for its alleged teaching of mass spectroscopy for the identification or novel protein-ligand interactions; while for Claim 49 Loo et al. was cited for its teaching of fragmentation of a protein-ligand conjugate via tandem mass spectroscopy.

Pitner et al. has been discussed above. Loo concerns the study of *non-covalent* protein complexes by electrospray ionization mass spectrometry.

The proposed combination of the cited references is legally improper, since neither reference has any motivation for the purported combination.

Since antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one reading the disclosure of Pitner et al. would not be motivated to search for any method for identifying the antigens present in the antigen-antibody complexes, given the fact that the antigens are known.

Furthermore, Pitner et al. disclose a *covalent* bond between an antibody and an

antigen, while Loo deals with the detection of *non-covalent* complexes. Therefore, one reading the disclosure of Pitner et al., even if for some reason the identification of the (already known) antigen were desirable, would not turn to Loo, addressing a completely different problem.

Furthermore, *even if the combination were legally proper, it would not render obvious the claimed invention*. As discussed above, Pitner et al. does not teach all elements of the invention claimed and thus does not anticipate Claims 40-41 and 44-46. Since Loo et al. does not supply the teaching missing from Pitner et al., the combination of the two references does not make obvious Claims 40-41 and 44-46. As a result, dependent Claims 47-49, which carry all limitations of the claims to which they refer, are not rendered obvious either.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

THE REJECTION UNDER 35 U.S.C. 103(a) OVER PITNER ET AL. AND GANEM ET AL. SHOULD BE WITHDRAWN

Claims 40-41, 44-48, and 56 were rejected under 35 U.S.C. 103(a) as "unpatentable" over Pitner et al. (U.S. Patent No. 5,367,058) and Ganem et al. (J. Am. Chem. Soc. 1991, 113(16), 6294-6).

Pitner et al. was applied as in the previous rejection. Ganem et al. was cited for Claims 47-49 as allegedly teaching the use of mass spectroscopy for identifying enzyme-substrate, receptor-ligand complexes. According to the rejection, it "would have been obvious to one skilled in the art at the time the invention was made to 'screen a library of small organic compounds' as taught by Pitner et al. in conjunction with the mass spectrometer techniques as taught by Ganem et al. because Ganem et al. explicitly states that the mass spectrometry 'can be applied to problems of biological interest [including] ...proteins and that the methods are good for 'detecting and identifying enzyme-substrate, receptor-ligand [complexes].'"

Applicants respectfully disagree.

For the same reasons discussed above, *the proposed combination of references is legally improper*.

Pitner et al. has been discussed above. In relevant part, it concerns modified antibodies and antibody fragments which display an increased affinity for the corresponding antigen. Ganem et al. propose the use of mass spectrometry for the detection of noncovalent molecular association complexes.

Since antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one reading the disclosure of Pitner et al. would not be motivated to search for any method for identifying the antigens ("ligands") bound to the antibodies of Pitner et al., given the fact that the antigens are known.

Furthermore, Pitner et al. disclose a *covalent bond* between an antibody and an antigen, while Ganem et al. deal with the detection of *non-covalent complexes*. Therefore, one reading the disclosure of Pitner et al., even if for some reason the identification of the (already known) antigen were desirable, would not turn to Ganem et al., addressing a completely different problem.

The references, even if combined, would not make obvious the claimed invention

Pitner et al., as discussed above, fails to disclosed all elements of the claimed invention. Since Ganem et al. does not supply the teaching missing from Pitner et al. the combinations of the two references does not make obvious the rejected claims.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

THE REJECTION UNDER 35 U.S.C. 103(a) OVER PITNER ET AL. AND PRZYBYLSKI ET AL. AND WUNSCH ET AL. SHOULD BE WITHDRAWN

Claims 40-41, and 44-52 were rejected as allegedly obvious over Pitner et al. (U.S. Patent No. 5,367,058) and Przybylski et al. (Angew. Chem. Int. Ed. Engl. 1996, 35, 806-826) and Wunsch et al. provided in the form of an excerpts from Greene, T.W. et al., referencing the Wunsch et al. article.

Pitner et al. was cited as discussed above. Przybylski et al. was cited for its teaching of mass spectrometry for the study of receptor-ligand interactions, including antibody-antigen interactions, and the identification of the ligand using mass spectrometry without purification. With regards to Claim 49, the Examiner cited Przybylski as allegedly teaching the use of fragmentation both by enzymatic and by mass spectrometry techniques. For Claims 50-52, Przybylski et al. was cited for its teaching of DTT.

The rejection is respectfully traversed.

Pinter et al. has been discuss in response to the previous rejections. Applicants have shown that Pitner et al. fails to teach all elements of the claimed invention, and therefore, contrary to the Examiner's assertion, does not anticipate Claims 40-41 and 44-46.

Przybylski et al. discusses the use of electrospray mass spectrometry of biomacromolecular complexes with non-covalent interactions. Just as in the previous rejections, *the purported combination of references is legally improper*, for essentially the same reasons as those discussed in the previous rejections. In brief, Pitner et al. concerns antibody-antigen interactions, where the identity of the antigen is known. Therefore, one skilled in the art would not be motivated to seek out techniques (e.g. mass spectrometry as taught by Przybylski et al.) to identify an antigen bound to an antibody. Furthermore, in Pitner et al. the antigen is *covalently* attached to the antibody. Przybylski et al. concerns the study of *non-covalent* interactions. Accordingly, even if the identification of the antigen bound to the antibody of Pitner et al. would be desirable, one skilled in the art would not look for the teaching of Przybylski et al.

Furthermore, *the references, even if combined, do not make obvious the claimed invention*. As discussed earlier, Pitner et al. does not disclose all elements of the invention as claimed in Claims 40-41 and 44-46. Przybylski et al. or Wunsch et al. (cited to show the state of the art with regard to disulfide bond cleavage) do not supply the teaching missing from Pitner et al. Accordingly, the cited combination of references does not make obvious the claims rejected, and the present rejection should be withdrawn.

THE REJECTION OF CLAIMS 40-41, 44-52, AND 56 UNDER 35 U.S.C. 103(a) OVER JANDA ET AL. AND PRZYBYLSKI ET AL. AND WUNSCH ET AL. SHOULD BE WITHDRAWN

Claims 40-41, 44-52, and 56 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Janda et al., *supra*, Przybylski et al., *supra*, and Wunsch et al., *supra.*

According to the rejection, Janda et al. teaches all the limitations of Claims 40-41, and 44-46. This is incorrect. As discussed earlier, the racemic reagent 1 of Janda et al. is not a ligand as ligands are defined in the present application. Although the reagent 1 of Janda et al. is coupled to BSA by a chemical reaction, it does not have an inherent affinity (binding ability) to BSA, therefore, it is not a "ligand" of BSA. Furthermore, even if reagent 1 were considered a ligand, Claim 40 would still not anticipated, since the racemic reagent 1 coupled to BSA does not contain a free chemically reactive group as claimed in the present application. Accordingly, Janda et al. does not disclose target protein-ligand conjugates, as defined in the present application, or any screening assays with such target protein-ligand conjugates.

The secondary references, which had been discussed in addressing the previous rejections, do not supply the teaching missing from Janda et al. Accordingly, the cited combination of references does not make obvious the claims rejected, and the present rejection should be withdrawn.

THE REJECTION OF CLAIMS 40-41, AND 44-53 UNDER 35 U.S.C. 103(a) OVER PITNER ET AL. AMD PRZYBYLSKI ET AL. AND CROOKE ET AL. SHOULD BE WITHDRAWN

Claims 40-41 and 44-53 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Pitner et al., *supra* and Przybylski et al., *supra* and Crooke et al. (U.S. Patent No. 6,428,956).

Pitner et al. and Przybylski et al. have been applied as in the previous rejections. Crooke et al. was cited against Claim 53, for its disclosure of the use of mass tags in

combinatorial screening techniques, which, according to the rejection, anticipates the "labeled probes" of Claim 53.

In addressing the previous rejections, Applicants have shown that neither Pitner et al. nor Przybylski et al. teach all elements of the invention as claimed in Claims 40-41 and 44-52. Indeed Pitner et al. or Przybylski et al., taken alone or in combination, does not disclose or suggest the screening of a library of small organic molecules with a target protein-ligand conjugate as claimed in the present application. Accordingly, the combination of these references does not make obvious Claims 40-41 and 44-52. Since the claims on which Claim 53, directly or indirectly, depends define unobvious processes, the process claimed in Claim 53 is also unobvious, regardless of the teaching of Crooke et al. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

THE REJECTION OF CLAIMS 40-41, 44-53 AND 56 UNDER 35 U.S.C. 103(a) OVER JANDA ET AL. AND PRZYBYLSKI ET AL. AND CROOKE ET AL. SHOULD BE WITHDRAWN

Claims 40-41, 44-53 and 56 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Janda et al., *supra*, and Przybylski et al. and Crooke et al.

As discussed in response to the previous rejections, Janda et al. discloses a the *covalent* binding of a small molecule (compound 1) to a target protein (BSA), but does not teach target protein-ligand conjugates as defined in the present application. Przybylski et al. discusses the use of electrospray mass spectrometry of biomacromolecular complexes with *non-covalent* interactions. Just as in the previous rejections, *the purported combination of references is legally improper*, for essentially the same reasons as those discussed in the previous rejections. One skilled in the art, reading the disclosure of Janda et al. would not be motivated to apply the teaching of Przybylski et al.

In addition, even if the combination were legally proper, it would still not make obvious the claims rejected. There is absolutely no teaching, suggestion or hint in the

two references, when taken alone or in combination, that would suggest the screening of a small organic molecule library with a target protein-ligand conjugate carrying a free reactive group, in order to identify ligands having inherent affinity for binding to the target protein, as claimed in the present application. Crooke et al. does not remedy the deficiencies of the other two references. Accordingly the cited combination of references does not make obvious the invention claimed in the rejected claims, and the present rejection should be withdrawn.

Double Patenting

Claims 40-41, 44-53, and 56 were rejected under the judicially created doctrine of obviousness-type double patenting as "unpatentable" over claims 1-39 of U.S. Patent Application Publication 2002/0022233 A1 and claims 1-39 of U.S. Patent Application Publication 2002/0081621 A1. This is a provisional obviousness-type double patenting rejection, since the conflicting claims are not in fact patented.

Without acquiescing to the present rejection, applicants believe that all other rejections have been overcome by the foregoing arguments. Accordingly, even if the present rejection is maintained, it should be withdrawn in the present application, and repeated in one or both of the pending parallel applications, where it can be properly addressed.

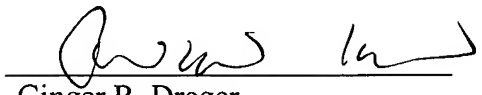
The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Should the Examiner find that there are any further issues outstanding, Applicants hereby request a personal interview. The Examiner is respectfully requested to contact the undersigned attorney to arrange the time for the interview.

The Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1C1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: May 19, 2003



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